

Remarks

A. Status of Claims/Amendments

Claim 21 has been amended. Claims 1-20, 22 and 30-32 have been canceled as discussed below. Thus, claims 21, 23-29 and 33-34 are pending.

Claim 21 has been amended to introduce the language “wherein said solid nanoparticles are formed by cooling the microemulsion without aqueous dilution.” Support for this language can be found in the specification at page 5, lines 14-17, again at page 7, lines 12-18 (and Figure 6), and lines 20-26 (Figure 6), and discussed in the Specification in Examples 8 and 9:

“Further, Method A [cooling the of the *undiluted* oil-in-water microemulsion] illustrated a key advantage of simply allowing the oil-in-water microemulsion to cool to room temperature to form useful solid nanoparticles. This method allows for rapid, reproducible and cost-effective method to engineer useful nanoparticles.” See page 32, line 24, to page 33, line 2; see also page 33, lines 12-19; see page 5, lines 14-17; see page 5, lines 23-25; see page 7, lines 20-26 and Figure 6; see also page 40, lines 25-28

B. Novelty

The Action first rejects claims 21, 23, 25, 27, 33 and 34 as anticipated by the Gasco reference. Applicants respectfully traverse.

With respect to Gasco, it is first noted that many Gasco publications are currently of record which have a virtually identical disclosure to that of the Gasco reference now cited. See, for example, Cavalli *et al.*, *Int. J. Pharmaceutics*, 182:59-69 (1999); Bocca *et al.*, *Int. J. Pharmaceutics*, 175:185-193 (1998). Both of these references, similar to the current Gasco reference (see top of middle column, page 53), require the use of at least 10 volumes of distilled cold water in order to “cool” the microemulsion. In addition, the Gasco patent (5,250,236)

referenced in the present application at page 5, lines 8-17, teach the dispersion of the microemulsion into cold aqueous medium at dilutions of 10 to 200 fold to prepare nanoparticles

Turning to the current Gasco reference, it is again noted that this reference also requires the use of a cold aqueous medium that is used to disperse the microemulsion (see top of middle column, page 53). However, the present inventors have discovered that the nanoparticles can be readily formed by cooling the microemulsion without the use of an aqueous dilution step. Thus, it is submitted that the claims, which refer to forming the nanoparticles “without the use of an aqueous dilution” clearly distinguish over the process described by Gasco, which requires such a step.

It is further noted that as disclosed in the Applicants’ specification, there are substantial advantages associated with cooling without the use of an aqueous dilution step, in that such a “method allows for rapid, reproducible and cost-effective method to engineer useful nanoparticles.” See page 32, line 24, to page 33, line 2; see also page 33, lines 12-19. Again, as noted in the specification in connection with Gasco, the inventors state that “Gasco does not teach the use of nanoparticles made from oil-in-water microemulsion precursors wherein said nanoparticles containing drugs are formed directly by cooling the oil-in-water microemulsion with no dilution of the most useful system.” Specification, page 5, lines 14-18. As further noted, such a process results in the ability to carry out the procedure “in a one-step process and contained in one manufacturing vessel, vial or container.” Specification, page 5, lines 24-25.

In contrast, the microemulsions prepared by Gasco must be “quenched and dispersed in cold aqueous medium (2-3°C) at a suitable ratio under mild mechanical stirring” to produce nanoparticles (page 53 under “Step 4”; page 53, Figure 1). Furthermore, since the Gasco method teaches that the emulsion must be “dispersed” into a second vessel comprising the cold aqueous

medium, Gasco necessarily requires that the microemulsion contained in one vessel be transferred to a second vessel, and thus cannot be performed in a single vessel. As we know from other Gasco publications discussed above, the Gasco dispersion step results in at least a 10-fold dilution of the microemulsion; thus, resulting in a 10-fold reduction in the resulting nanoparticle concentration. This requires substantial additional manipulation of the resulting very dilute composition, including, for example, lyophilization.

However, the present inventors discovered that in their most useful and convenient system, solid nanoparticles could be produced without using aqueous dilution, for example, to cool the microemulsion. This permits one to produce more concentrated nanoparticles and the process can be carried out, where desired, as a one-step process and contained, where desired, in one manufacturing vessel, vial, or container. Methods to manufacture pharmaceutical nanoparticles that can be used to produce a concentrated system directly and that may be performed without additional steps to reconcentrate diluted systems have significant economical and practical advantages. For example, steps to reconcentrate nanoparticles may be expensive and time-consuming, and have increased potential for contaminating the final product with unwanted materials or bioburden during the additional required steps. Of course, the foregoing is described in order to demonstrate the significant advantages to the presently claimed invention, and is not intended to exclude the possibility of, for example, lyophilization or even adding small amounts of water for purposes other than cooling the microemulsion to form the solid nanoparticles.

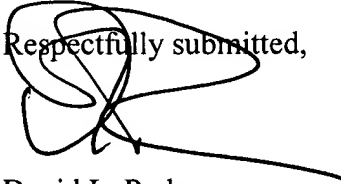
C. Obviousness

The Action next rejects the remaining claims, claims 24, 26, 28 and 29, over Gasco, with the Action stating that these dependent claims merely set forth specific concentrations of active ingredients that are not seen as conferring patentability absent a showing of criticality.

In response, Applicants direct the Examiner to the discussion above with respect to Gasco, which discussion is believed to be equally applicable to the present rejection.

D. Conclusion

Applicant believes that this Submission fully responds to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn so the claims may swiftly pass to issuance. Please contact the undersigned attorney at 512-536-3055 with any questions.

Respectfully submitted,


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